

## Reply to M Amiri et al.

Dear Editor:

We appreciate you for providing us with the opportunity to discuss our recent article (1) regarding the concerns brought forward by Amiri et al. We also thank Amiri et al. for bringing these issues to our attention.

Amiri et al. commented on the eligible publications that had not been included. However, as mentioned in the Methods section of the published article, only studies on the effect of flaxseed as whole flaxseed, flaxseed oil, or flaxseed lignans were included in our analysis. Amiri et al. mentioned 5 studies (2–6) that they think we should have included. These 5 studies were present in our initial search, but were later excluded because of the following reasons. In 3 articles (2, 3, 5), flaxseed was administered with another intervention, which was not adjusted for. This was one of our main exclusion criteria. In 2 studies (4, 6), information on inflammatory factors was unavailable and we did not receive any answers despite sending several emails to the corresponding authors.

Amiri et al. also questioned the search strategy. Although our search strategy was selected based on a past meta-analysis (7), we reperformed the search process using the search strategy proposed by Amiri et al. up to May 2018. As a result, the number of obtained articles from the new search was exactly the same as for the previous one and no new studies were found.

The third comment raised by Amiri et al. was related to the inclusion and exclusion criteria. They noted that the study carried out by Ricklefs-Johnson et al. (8) should not have been included in our analysis. In this regard, we should mention that the results of Table 1, e.g., the calorie contents of the ground flaxseed and psyllium, were not of particular relevance to our study. Furthermore, the changes in nutrient intakes (amounts of energy, total fat, fiber, and sodium) were not significantly different ( $P > 0.05$ ) between the ground flaxseed and psyllium groups (Table 3). In addition, the sensitivity analysis indicated no significant changes in the results after removing the research conducted by Ricklefs-Johnson et al. (9). Therefore, in our opinion, this study should not be excluded.

Another objection raised by Amiri et al. related to the effect size calculation. This can be justified by mentioning that although some references suggested reporting 1 effect size from each study, others included  $>1$  effect size, which is similar to our method (10–12). Moreover, studies with  $>1$  effect size, such as the one by Machado et al., compared 2 separate intervention groups with 1 control group. However, our aim was to investigate the effect of different doses of flaxseed by performing subgroup analysis. Given that application of different effect sizes from 1 study is a routine

approach used in numerous meta-analyses, its inclusion in our study did not impair the accuracy of results.

Finally, we do not agree with Amiri et al. regarding their last comment. In our analysis, different types of flaxseed including brown, golden, flaxseed oil, and lignans were analyzed. Moreover, the results analyzed the subgroup types of flaxseed in the subgroup analysis, which is in line with previous similar meta-analyses (7, 13).

We thank Amiri et al. for their letter regarding our publication and look forward to future research on this exciting topic.

Mehran Rahimlou  
Nasrin Banaie Jahromi  
Nazila Hasanyani  
Amirhossein Ramezani Ahmadi

From the Department of Nutrition, School of Para-Medical Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (MR, e-mail: [rahimlum@gmail.com](mailto:rahimlum@gmail.com); NB; ARA); Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (MR; NB); Emam Reza Hospital affiliated with Social Security Organization, Urmia, Iran (NH); and Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (ARA).

The authors reported no funding received for this work.

Author disclosures: The authors report no conflicts of interest.

## References

1. Rahimlou M, Jahromi NB, Hasanyani N, Ahmadi AR. Effects of flaxseed interventions on circulating inflammatory biomarkers: a systematic review and meta-analysis of randomized controlled trials. *Adv Nutr* 2019;10(6):1108–19.
2. Cassani RSL, Fassini PG, Silvah JH, Lima CMM, Marchini JS. Impact of weight loss diet associated with flaxseed on inflammatory markers in men with cardiovascular risk factors: a clinical study. *Nutr J* 2015;14(1):5.
3. Nelson TL, Stevens JR, Hickey MS. Inflammatory markers are not altered by an eight week dietary  $\alpha$ -linolenic acid intervention in healthy abdominally obese adult males and females. *Cytokine* 2007;38(2):101–6.
4. Schwab US, Callaway JC, Erkkilä AT, Gynther J, Uusitupa MI, Järvinen T. Effects of hempseed and flaxseed oils on the profile of serum lipids, serum total and lipoprotein lipid concentrations and haemostatic factors. *Eur J Nutr* 2006;45(8):470–7.
5. Almario RU, Karakas SE. Lignan content of the flaxseed influences its biological effects in healthy men and women. *J Am Coll Nutr* 2013;32(3):194–9.
6. Tint D, Anghel M, Lupu DS, Fischer LM, Niculescu MD. Low dose flaxseed oil supplementation alters the fatty acids profile and the progression of metabolic syndrome in men without adequate medical treatment. *J Nutrition Disorder Ther* 2011;S7:001.
7. Ren GY, Chen CY, Chen GC, Chen WG, Pan A, Pan CW, Zhang YH, Qin LQ, Chen LH. Effect of flaxseed intervention on inflammatory marker C-reactive protein: a systematic review and meta-analysis of randomized controlled trials. *Nutrients* 2016;8(3):136.
8. Ricklefs-Johnson K, Johnston CS, Sweazea KL. Ground flaxseed increased nitric oxide levels in adults with type 2 diabetes: a randomized comparative effectiveness study of supplemental flaxseed and psyllium fiber. *Obes Med* 2017;5:16–24.

9. Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions*. Chichester, UK: John Wiley & Sons; 2011.
10. Zarezadeh M, Khorshidi M, Emami M, Janmohammadi P, Kord-Varkaneh H, Mousavi SM, Mohammed SH, Saedisomeolia A, Alizadeh S. Melatonin supplementation and pro-inflammatory mediators: a systematic review and meta-analysis of clinical trials. *Eur J Nutr* 2019 (Epub ahead of print, DOI:10.1007/s00394-019-02123-0).
11. Rezagholizadeh F, Keshavarz SA, Djalali M, Rad EY, Alizadeh S, Javanbakht MH. Vitamin D3 supplementation improves serum SFRP5 and Wnt5a levels in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *Int J Vitam Nutr Res* 2018; 88(1–2):73–9.
12. Ramezani Ahmadi A, Rayyani E, Bahreini M, Mansoori A. The effect of glutamine supplementation on athletic performance, body composition, and immune function: a systematic review and a meta-analysis of clinical trials. *Clin Nutr* 2019;38(3):1076–91.
13. Mohammadi-Sartang M, Mazloom Z, Raeisi-Dehkordi H, Barati-Boldaji R, Bellissimo N, Totasy de Zepetnek JO. The effect of flaxseed supplementation on body weight and body composition: a systematic review and meta-analysis of 45 randomized placebo-controlled trials. *Obes Rev* 2017;18(9):1096–107.